REMARKS

Claims 1-626 are pending in this application. Of these, claims 1-250, 288-624 and 626 are believed to have been withdrawn from consideration as being drawn to non-elected inventions. Claims 251-285 and 625 are presently under examination. In the claims listing above, claim 251 has been amended. Further, the claims previously withdrawn from consideration, 1-250, 288-624 and 626, have been canceled above. No claims have been added by this paper. Accordingly, as reflected in the claim listing above, claims 251-285 and 625 are presented for further examination.

Claim Amendments

As just indicated, claim 251 has have been amended. In claim 251, the phrase "Universal Detection Target" has been inserted before "UDT" as required by the Examiner in the August 6, 2007 Office Communication.

Entry of the above claim amendments is respectfully requested.

Amendments to the Specification & Figures

The specification and figures have also been amended as required by the Examiner. Various nucleic acid sequences greater than 10 nucleotides in length have now been identified by appropriate SEQ ID numbers on pages 33, 37 and 41. A copy of each of amended pages 33, 37 and 41 are provided in Exhibit A. Similarly, Figures 4 and 5 have been amended to recite appropriate SEQ ID numbers with corresponding changes having been made to the "Brief Description of the Drawings" section. A copy of each of amended Figures 4 and 5, and also amended page 4 ("Brief Description of the Drawings") are provided as Exhibit B.

Entry of the foregoing amendments to the specification and figures is respectfully requested.

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Application Re-Assignment

Applicants and their attorneys acknowledge the reassignment of this application to Examiner Angela Bertagna, Group Art Unit 1637.

Priority

The Examiner's comments regarding the priority date for this application is acknowledged. Applicants understand that the instant October 24, 2003 filing date has been used for prior art purposes.

Objections to the Specification

The specification has been objected to according to the August 6, 2007 Office Communication (page 3):

> 3. The disclosure is objected to because of the following informalities: The specification recites nucleic acid sequences greater than 10 nucleotides in length that are not identified by the appropriate SEQ ID number on pages 34, 38, and 42. Also, Figures 4 and 5 recite nucleic acid sequences greater than 10 nucleotides in length that are not identified by the appropriate SEQ ID number either in the figure or in the "Brief Description of the Drawings" section.
>
> Appropriate correction is required.

As indicated earlier, pages 4, 33, 37 and 41 in the specification and Figures 4 and 5 have been appropriately corrected to reflect SEQ ID numbers for various nucleic acid sequences greater than 10 nucleotides in length.

In light of the foregoing amendments, withdrawal of the objection is respectfully requested.

Claim Objection

Claims 251-287 stand objected to because of an informality. According to the Office Communication (page 3): "These claims recite "a non-inherent UDT." The acronym UDT should be written out prior to its use as an acronym in order to clarify the

claim language. Appropriate correction is required."

As also indicated earlier, claim 251 has been amended by inserting "Universal Detection Target" before the first recitation of "UDT."

In light of the amendment to claim 251, Applicants respectfully request reconsideration and withdrawal of the claim objection.

Turning now to the obviousness rejections . . .

Commonality of Ownership

Applicants assert that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made.

The First Rejection Under 35 USC §103

Claims 25 1-264, 269-273, 275, 28 1-286, and 625 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1 201768 A2; newly cited). According to the Office Communication (page 9):

> It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Laird to the method taught by Lin. An ordinary practitioner would have been motivated to modify the primers taught by Lin to include the modified nucleotides (2'-O-methyl-nucleotides, 2'-fluoro-nucleotides, and 2'-amino-nucleotides) taught by Laird at the 3' terminus, since Laird taught that the presence of these modified nucleotides at the 3' terminus of an amplification primer reduced nonspecific amplification (paragraph 37). Combining the teachings of Lin and Laird would result in placement of at least one of the nucleotide analogs in the homopolymeric sequence comprising the 3' oligo(dT) tail of the primer taught by Lin. An ordinary practitioner would have had a reasonable expectation of success applying the teachings of Laird to the method taught by Lin since Laird taught that the synthesis of primers containing the modified nucleotides was conducted using commercially available reagents and standard chemical synthesis methods known in the art (paragraphs 41-45). Thus, the method of claims 25 1-264, 269-273. *275.* 281-286, and 625 is prima facie obvious in view of

the combined teachings of Lin and Laird.

The first obviousness rejection is respectfully traversed.

The present invention is principally directed to a method of synthesizing one or more copies of a library of nucleic acid targets. In the first step of the method, the following are provided: (i) a library of nucleic acid targets, (ii) primers or nucleic acid constructs comprising sequences complementary to homopolymeric sequences in the library of nucleic acid targets (the primers or nucleic acid constructs comprising one or more terminal nucleotides at their 3′ ends, such terminal nucleotides comprising nucleotide analogues with substitutions on the 2′ position of the ribose ring), (iii) synthesizing reagents for the synthesis of a nucleic acid copy; and (iv) addition reagents for the addition of a non-inherent Universal Detection Target (UDT). Following annealing of the primers or nucleic acid constructs to the homopolymeric sequences in the library of nucleic acid targets, the annealed primers or constructs are extended using the synthesizing reagents and then adding a non-inherent UDT to the extended primers or constructs.

In response to the obviousness rejection at hand, Applicants respectfully point out that a person of ordinary skill in the art would not have been motivated to combine the Lin and Laird disclosures as suggested in the rejection. Indeed, there are several significant reasons why this is so.

First, the primary Lin reference is directed to library amplification whereas the secondary Laird reference is confined to specific amplification. More particularly, Lin et al. describe library amplification wherein any and all of their disclosed poly A mRNAs are used for template dependent amplification. In contrast to the primary reference, Laird et al. use PCR for specific amplification of one or a few unique species. Even when Laird offers alternative methods such as strand displacement, transcription-based amplification and self-sustained sequence replication, all such alternative methods share the common feature of being primarily limited to a single

target sequence. Thus, all of Laird's disclosed amplification methods are solely directed to specific amplification.

Second, and an equally important reason why the two cited disclosures are not properly combinable concerns the primers used separately by Laird and Lin. In the case of the former, Laird is solving a problem where both forward primers and reverse primers are present in the amplification reaction. Nonspecific binding of one primer to another primer leads to exponential amplification (the so-called "primer-dimer problem). In contrast, Lin et al. have only a single primer present when the poly A mRNA is copied and transformed into cDNA. A second primer is only present after the initial (forward) primer has been removed. As such, no exponential primer-dimer fraction is present during global mRNA amplification. Thus, the problem described by Laird et al. does not even exist in the case of Lin et al. (or the present invention for that matter) because the latter do not have exponential amplification with target-derived or target independent extension products. Thus, an approach or solution for specific amplification where two primers (primer-dimer) are employed would not, in the eyes of the ordinarily skilled artisan, be deemed properly combinable with a library amplification that involves a single extension event.

Third, it should be pointed out that the common understanding behind primer-dimer generation is that this product is the result of rare events where a primer uses a different primer as a template. It is only due to the power of PCR amplification that these rare events become a significant product.

Fourth and finally, the theory that is offered by Laird for the ability of the nucleotide's action is in line with stepwise events of PCR, i.e., the presence of the analogues slows down the efficiency of extension on an incorrect template. In PCR this delay can have functionality because PCR involves timed steps where if an extension event has not taken place during the extension phase of the cycles, the subsequent denaturation step removes the unextended primer from the template. As a consequence, an extension event would now require another binding step to

take place before there is a mis-priming. In linear methods of amplification (such as those of the present claims), the substrates are kept together for extended periods and a delay in extension would be seen to have only minimal effects. Thus, a reading of Laird's explanation would not invite the ordinarily skilled user to apply the use of the modified primers of Laird to the system described by Lin.

In light of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the first obviousness rejection.

The Second Rejection Under 35 USC §103

Claims 265-268 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1201768; newly cited) and in further in view of Willis et al. (US 6,858,412; newly cited) and further in view of Moran et al. (Nucleic Acids Research (1996) 24(11): 2044-2052; newly cited). According to the Office Communication (page 11):

> It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Willis and Moran to the method resulting from the combined teachings of Lin and Laird. An ordinary practitioner would have been motivated to include a terminator nucleotide, such as the dideoxy or acyclic nucleotides taught by Willis, in the terminal transferase tailing reaction taught by Lin, since Willis taught that these nucleotides prevented polymerase-mediated extension, and also since Moran taught that terminator nucleotides reduced template-independent addition of 3' terminal nucleotides by DNA and RNA polymerases (see column 46, lines 40-45 of Willis and pages 2044-2045 of Moran). An ordinary practitioner would have been particularly motivated to minimize template-independent addition of nucleotides by the polymerase since Moran taught that such addition "complicates purification, may interfere with subsequent reactions, such as ligation, and wastes nucleotide substrates (page 2044, column 2)." An ordinary practitioner would have had a reasonable expectation of success in including dideoxy or acyclic nucleotides in the terminal transferase reaction thught by Lin since Willis taught that terminal transferase could incorporate these nucleotides into nucleic acids (column 26, lines 40-45). Thus, the

> methods of claims 265-268 are prima facie obvious in view of the combined teachings of Lin, Laird, Moran, and Willis.

The second obviousness rejection is respectfully traversed.

In response and at the outset, Applicants incorporate and reiterate their remarks above (pages 13-15) in regard to the first obviousness rejection based upon Lin et al. as a primary reference and Laird et al. as a secondary reference. Those remarks concern:

- the nature of the amplification being sought (library amplification in Lin's case and specific amplification in Laird's case)
- the primers used and extension products (single primer, single extension products in Lin's case and two primers, exponential amplification in Laird's case)
- primer-dimer generation is rare and only becomes significant in PCR
- Laird's explanation regarding analogs would not invite application to Lin's system

It is believed that the inclusion of Willis et al. and Moran et al. as further references to Lin et al. and Laird et al. would not cure the deficiencies in the latter two documents which are not properly combinable.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the second obviousness rejection.

The Third Rejection Under 35 USC §103

Claims 274 and 276 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Lin et al. (US 6,197,554 BI; cited previously) in view of Laird et al. (EP 1201768; newly cited) and further in view of Sousa et al. (US 5,849,546; newly cited). According to the Office Communication (page 13):

> It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Sousa to the method resulting from the combined teachings of Lin and Laird.

> An ordinary practitioner would have been motivated to utilize the mutant RNA polymerase taught by Sousa to generate chimeric DNA/RNA transcripts since Sousa taught that such transcripts displayed improved resistance to ribonucleases (column 8, lines 55-67). An ordinary practitioner would have recognized that RNase degradation of the transcription product produced in step d of the method outlined in Figure 1 of Lin would be detrimental since the method of Lin required a post-transcription PCR amplification step, and therefore, would have been motivated to minimize the possibility of such degradation by generating a chimeric DNA/RNA transcript as suggested by Sousa. Thus, the methods of claims 274 and 276 are prima facie obvious in view of the combined teachings of Lin, Laird, and Sousa.

The third obviousness rejection is respectfully traversed.

In response, Applicants adopt their remarks on pages 13-15 with respect to Lin et al. and Laird et al. It is believed that the inclusion of Sousa et al. as a tertiary reference does not cure the deficiencies in the Lin et al. and Laird et al. which are not properly combinable.

In light of the foregoing, Applicants respectfully request reconsideration and withdrawal of the third obviousness rejection.

The Fourth Rejection Under 35 USC §103

Claims 277, 278, and 280 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Lin et al. (US 6,197,554 81; cited previously) in view of Laird et al. (EP 1201768; newly cited) and further in view of Steffens et al. (Genome Research (1995)5:393-399; newly cited). According to the Office Communication (pages 14-15):

> It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize the fluorescently labeled nucleotide taught by Steffens in the method resulting from the combined teachings of Lin and Laird. An ordinary practitioner would have been motivated to utilize the nucleotide taught by Steffens to label transcription products generated by the method resulting from the combined teachings of Lin and Laird, since Steffens taught that

labeling nucleic acids with this nucleotide permitted highly sensitive detection with minimal background (page 394, column 1). Also, as noted in MPEP 2144.07, selection of a known material based on its suitability for the intended purpose is prima facie obvious. An ordinary practitioner would also have been motivated to label nucleic acid products generated at any point in the method resulting from the combined teachings of Lin and Laird (e.g. the final RT-PCR step) in order to monitor the yield at each step of the process. An ordinary practitioner would have been motivated to do since Lin taught labeling nucleic acid products produced al multiple steps of the method (see columns, lines 19-23). As noted above, an ordinary practitioner would have been motivated to utilize the fluorescently labeled nucleotide taught by Steffens to conduct this labeling step, since Steffens taught that the nucleotide permitted sensitive detection of labeled nucleic acids with minimal background. An ordinary practitioner would have had a reasonable expectation of success in using the fluorescently labeled nucleotide taught by Steffens since Steffens expressly taught its use in PCR amplification (page 397, column 2). Thus, the methods of claims 277, 278, and 280 are prima facie obvious in view of the combined teachings of Lin, Laird, and Steffens.

The fourth obviousness rejection is respectfully traversed.

In response, Applicants adopt and reiterate their remarks on pages 13-15 with respect to Lin et al. and Laird et al. It is believed that the further inclusion of Steffens et al. does not cure the deficiencies in Lin et al. and Laird et al., the latter two documents not being properly combinable.

Reconsideration and withdrawal of the fourth obviousness rejection is respectfully requested.

The Fifth Rejection Under 35 USC §103

Claim 279 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1201768; newly cited) and further in view of Sousa et al. (US 5,849,546; newly cited) and further in view of Steffens et al. (Genome Research (1995) 5: 393-399; newly cited). According to the Office Communication (pages 15-16):

> It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize the fluorescently labeled nucleotide taught by Steffens in the method resulting from the combined teachings of Lin, Laird, and Sousa. An ordinary practitioner would have been motivated to utilize the nucleotide taught by Steffens to label transcription products generated by the method resulting from the combined teachings of Lin. Laird, and Sousa, since Steffens taught that labeling nucleic acids with this nucleotide permitted highly sensitive detection with minimal background (page 394, column 1). Also, as noted in MPEP 2144.07, selection of a known material based on its suitability for the intended purpose is prima facie obvious. An ordinary practitioner would have had a reasonable expectation of success in using the nucleotide taught by Steffens since Sousa taught that the mutant RNA polymerase was capable of incorporating several different types of modified nucleotides (see column 9, lines 21-40). Thus, the method of claim 279 is prima facie obvious in view of the combined teachings of Lin, Laird, Sousa and Steffens.

The fifth obviousness rejection is respectfully traversed.

In response, Applicants again adopt and reiterate their remarks on pages 13-15 with respect to Lin et al. and Laird et al. It is believed that the inclusion of Sousa et al. and Steffens et al. as additional references does not cure the deficiences in Lin et al. and Laird et al. which are not properly combinable in any case.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the fifth obviousness rejection.

The Sixth Rejection Under 35 USC §103

Claim 287 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et a]. (US 6,197,554 Bl; cited previously) in view of Laird et al. (PP 1201768; newly cited) and further in view of Borson et al. (PCR Methods and Applications (1992)2: 144-148; newly cited). According to the Office Communication (page 17):

> It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Borson to

> the method resulting from the combined teachings of Lin and Laird. An ordinary practitioner would have been motivated to further include additional 3′ terminal nucleotides that were different from the homopolymeric sequence in the oligo(dT) primers taught by Lin since Borson taught that these additional 3′ terminal nucleotides locked the primer at the beginning of the poly(A) tail, thereby improving the homogeneity of the resulting cDNA population (see pages 144-146, cited above). An ordinary practitioner would also have been motivated to substitute these 3′ terminal nucleotides with nucleotide analogues containing modifications at the 2′ position of the ribose ring since Laird taught that these modifications reduced nonspecific amplification (paragraph 37). An ordinary practitioner would have had a reasonable expectation of success in applying the teachings of Borson to the method resulting from the combined teachings of Lin and Laird, since Borson taught that a degenerate set of "lock docking" primers could he used together to amplify cDNA from a diverse mRNA population (page 148). Thus the method of claim 287 is prima facie obvious in/view of the combined teachings of Lin, Laird, and Borson.

The sixth obviousness rejection is respectfully traversed.

In response, Applicants adopt and reiterate their remarks on pages 13-15 with respect to Lin et al. and Laird et al. It is believed that the inclusion of Borson et al. as a tertiary reference to Lin et al. and Laird et al. does not cure the deficiencies in the latter two which are not in any case properly combinable.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the sixth obviousness rejection.

The Seventh Rejection Under 35 USC §103

Claim 625 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Borson et al. (PCR Methods and Applications (1992) 2: 144-148; newly cited) in view of Laird et al. (EP 1201768; newly cited). According to the Office Communication (page 19):

> It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Laird to the method taught by Borson. An ordinary practitioner would have been motivated to modify the primer taught by Borson to include the

modified nucleotides (2'-O-methyl-nucleotides, 2'-fluoro-nucleotides, and 2'-amino-nueleotides) taught by Laird at the 3' terminus, since Laird taught that the presence of these modified nucleotides at the 3' terminus of an amplification primer reduced nonspecific amplification (paragraph 37). An ordinary practitioner would have had a reasonable expectation of success applying the teachings of Laird to the method taught by Borson since Laird taught that the synthesis of primers containing the modified nucleotides was conducted using commercially available reagents and standard chemical synthesis methods known in the art (paragraphs 41-45). Thus, the method of claim 625 is prima facie obvious in view of the combined teachings of Borson and Laird.

The seventh obviousness rejection is respectfully

In response, Applicants note that the primary Borson reference is also directed to a global copying of any and all mRNAs whereas the secondary Laird reference is confined to specific amplification of discrete sequences. As discussed earlier in response to the first obviousness rejection, when Laird offers alternative methods such as strand displacement, transcription-based amplification and self-sustained sequence replication, all such alternative methods share the common feature of being primarily limited to a single target sequence. Thus, all of Laird's disclosed amplification methods are solely directed to specific amplification.

Second, and an equally important reason why the two cited disclosures are not properly combinable concerns the primers used separately by Borson and Laird. In the case of the latter, Laird is solving a problem where both forward primers and reverse primers are present in the amplification reaction. Nonspecific binding of one primer to another primer leads to exponential amplification (the so-called "primer-dimer problem). In contrast, Borson et al. have only a single primer present when the poly A mRNA is copied and transformed into cDNA. As such, no exponential primer-dimer fraction is present during global mRNA amplification. Thus, the problem described by Laird et al. does not even exist in the case of Borson et al. (or the present invention for that matter) because the latter do not have exponential amplification with target-derived or target

independent extension products. Thus, an approach or solution for specific amplification where two primers (primer-dimer) are employed would not, in the eyes of the ordinarily skilled artisan, be deemed properly combinable with a library amplification that involves a single extension event.

Third, it should be pointed out that the common understanding behind primer-dimer generation is that this product is the result of rare events where a primer uses a different primer as a template. It is only due to the power of PCR amplification that these rare events become a significant product.

Fourth, the theory that is offered by Laird for the ability of the nucleotide's action is in line with stepwise events of PCR, i.e., the presence of the analogues slows down the efficiency of extension on an incorrect template. In PCR this delay can have functionality because PCR involves timed steps where if an extension event has not taken place during the extension phase of the cycles, the subsequent denaturation step removes the unextended primer from the template. As a consequence, an extension event would now require another binding step to take place before there is a mis-priming. In Borson's method, the substrates are kept together for extended periods and a delay in extension would be seen to have only minimal effects. Thus, a reading of Laird's explanation would not invite the ordinarily skilled user to apply the use of the modified primers of Laird to the system described by Borson et al.

Finally, the only thing that Borson et al. could possibly add is disclosure for an anchored primer to insure that priming of a poly A template takes place at the junction where the heterologous mRNA sequence is joined to the poly A tail. This does not invite the person of ordinary skill in the art to apply Laird's disclosure to Borson's method.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the seventh obviousness rejection.

* * * * * * *

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SUMMARY AND CONCLUSIONS

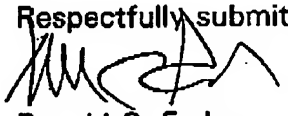
A complete listing of the claims in this application are provided above. In the complete listing above, claim 251 has been amended, and claims claims 1-250, 288-624 and 626 have been canceled as being directed to non-elected invention(s).

No fee or fees are believed due for this paper, apart from the Request For Extension Of Time (2 Months) and authorization for the small entity fee therefor. In the event that any other fee or fees are due, however, authorization is hereby given to charge the amount of any such fee(s) to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Early and favorable action is respectfully requested.

Respectfully submitted,



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